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Dockets Management Branch (HFA - 305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

RE: Draft Guidance for Industry on BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Postapproval Changes: Chemistry, Manufacturing and Controls Documentation
Docket No. [98D-0994]

Abbott Laboratories submits the following remarks in response to the Agency's request for comments on the above-named subject and docket. Abbott is an integrated worldwide manufacturer of healthcare products employing more than 56,000 people around the world with manufacturing sites in 35 countries.

We are pleased to have the opportunity to provide comments on the Draft Guidance for Industry and propose the attached modifications to the text. The format of our commentary includes the use of sections on comments and recommendations. The comment section provides a rationale for change while the recommendation section details the proposed changes and additions to current text. The format of the recommendations section shows additions to current text in *italics* and deletions to current text are shown in a ~~strike through~~ fashion.

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The final promulgation and implementation of this draft guideline should be undertaken in conjunction with an industry-wide educational effort for the following reasons:

- A. General educational purposes. Due to the broad scope of this proposal, any seminars on the final guidance will help everyone concerned. Such activities could be carried out with the support of FDLI, AAPS, DIA or other scientifically-oriented trade association.
- B. Publicity. The impact of this guidance may affect regulatory practices and expectations of manufacturers. By carrying out these seminars, the Agency can publicize and prepare all concerned for the new requirements.
- C. Clarity. Finally, public seminars will serve to clarify regulatory expectations and interpretations.

Yours truly,

A handwritten signature in black ink, appearing to read "F. Pokrop", written in a cursive style.

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cc: David R. Newkirk, FDA, HFV-142
Kasturi Srinivasachar, FDA, HFD-110

BACPAC I: Intermediates in Drug Substance Synthesis

Lines 7-8 **Comment:** Document exclusively uses the term *drug substance* without reference to the ICH-sponsored term *active pharmaceutical ingredient* or *API*.

Recommendation: Specify that drug substance is analogous to active pharmaceutical ingredient for harmonization purposes or replace drug substance with API throughout document.

Line 123: **Comment:** Ten historical batches may not be available. Document does not specify if equivalence studies with less than 10 historical batches will be acceptable without consultation. Revise text as follows.

Recommendation: The level of impurities should be assessed by comparing three postmodification batches to the range of historical data from *a minimum of 3 premodification batches (10 batches preferred when data are available)*.

Lines 128-130 **Comment:** For clarity, the following revision is offered:

Recommendation: The *intermediate* impurity profile will be considered equivalent after a given change if at least 3 postmodification batches of either 1). ~~a~~ current or subsequent isolated intermediate or 2). the drug substance are evaluated and the test data demonstrate that for:

Line 132: **Comment:** To reinforce that the impurity profile comparison can occur at the first intermediate following the change or any subsequent intermediate, the following text should be added.

Recommendation: No new impurity is observed at or above 0.1 percent *at current or subsequent isolated intermediate*.

Line 137: **Comment:** Including residual organic solvents in the text is redundant with impurity definition in glossary section which defines as any component of the drug substance that is not the entity defined as the drug substance. Revise text as follows:

Recommendation: Existing impurities, ~~including residual organic solvents,~~ are at or below the upper statistical limit of historical data.

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- Line 139:** **Comment:** Evaluation of total impurities with statistics may not be appropriate. The following text should be added.
- Recommendation:** Total impurities *are within established limits or* are at or below the statistical limit of historical data.
- Lines 173-177** **Comment:** Information is redundant with that provided in Lines 16-17. Delete this bullet point.
- Recommendation:** ~~Additional purification procedures (or repetition of an existing procedure on a routine basis) to achieve equivalence with prechange material after the final intermediate are not covered under BACPAC I. However, modified purification procedures prior to the final intermediate can be filed under BACPAC I (see section IV.C. for process changes and section IV.D. for multiple changes).~~
- Lines 197-200** **Comment:** Physical properties of the drug substance, when relevant to the final product dosage form, are typically included as drug substance specification(s). For comparative purposes, conformance to established drug substance acceptance criteria for physical properties should only be required. Revise text as follows:
- Recommendation:** ~~Conformance to established acceptance criteria for morphic form or, where acceptance criteria do not exist, the isolation of the same form or mixture of forms within the range of historical data, and conformance to historical particle size distribution profile.~~
- Lines 227&262** **Comment:** Site changes within a single facility needs further definition. It is our understanding of this section that for manufacturers with multiple buildings located in one facility, movement of the process from one building to another within that facility, can be made and if all requirements as outlined in section IV.A., as well as similar environmental controls and compliance to cGMP are met, no filing with the Agency is required.
- Recommendation:** Define facility.

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Lines 264-265: **Comment:** The filing of a site change to a contract manufacturer previously approved in the application for the manufacturing step(s) being transferred in an annual report is redundant since this data was evaluated at the time of the original submission. Recommend striking this requirement.

Recommendation: Annual Report if the site change does not involve the final intermediate and the new site is owned by either the applicant ~~or by a contract manufacturer previously approved in the application for the manufacturing step(s) being transferred.~~

Lines 321-323: **Comment:** The use of examples here is inconsistent with the format of the remainder of the document. Recommend striking the examples.

Recommendation: If new equipment is significantly different from that previously used, the potential for a change in the impurity profile exists even when there are no modifications to the process parameters. ~~Examples include switching from glass to metal reactors or changing the method of agitation for a step that depends on the mixing of heterogeneous materials.~~ A significant change of equipment should be filed as an amendment(s) to the master file(s) and/or in an annual report, as appropriate, and documented as described for scale changes.

Lines 341&358: **Comment:** The requirement to file the replacement of an existing analytical method with a new method that does not qualify as an improvement as a CBE is restrictive. If a method is deemed equivalent, and may provide improved assay time or cost, the guidance should allow for the change to be reported in an annual report. Revise text as follows:

Recommendation: Revise text as follows:

Line 341: Replacing an existing analytical method with an improved *or equivalent* method.

Line 358: Replacing an existing analytical method with a new method that does not qualify as an improvement *or as equivalent*.

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Lines 503-505: **Comment:** The requirement to submit a change control protocol for approval of changes to a starting material supplier's process in this context is inconsistent with the requirements for other material suppliers. Recommend striking this requirement.

Recommendation: ~~An outline of the change control protocol that has been or will be followed when establishing the suitability of a new supplier or when the existing supplier's process has changed.~~

Lines 589-593 **Comment:** Ten historical batches may not be available. Document does not specify if equivalence studies with less than 10 historical batches will be acceptable without consultation. Revise text as follows:

Recommendation: Data on impurities or physical attributes from a *minimum of 3 premodification batches representative of the established process (10 batches preferred when data are available).*

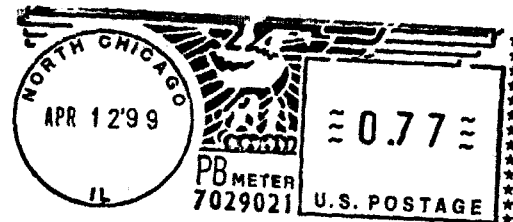
Lines 640-643: **Comment:** For consistency with other guidance documents (*i.e.*, ICH Q3A: Impurities in New Drug Substances, January 1996 and The Manufacture, Processing or Holding of Active Pharmaceutical Ingredients *Draft*, March 1998), the definition of starting material should be revised for consistency. See definition as follows:

Recommendation: *A material used in the synthesis of a drug substance (API) which is incorporated as an element into the structure of an intermediate and/or of the drug substance (API). Starting materials normally are commercially available and of defined chemical and physical properties and structure.*



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